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Memory as a new therapeutic target

Karim Nader, PhD; Oliver Hardt, PhD; Ruth Lanius, MD, PhD



This review aims to demonstrate how an understanding of the brain mechanisms involved in memory provides a basis for: (i) reconceptualizing some mental disorders; (ii) refining existing therapeutic tools; and (iii) designing new ones for targeting processes that maintain these disorders. First, some of the stages which a memory undergoes are defined, and the clinical relevance of an understanding of memory processing by the brain is discussed. This is followed by a brief review of some of the clinical studies that have targeted memory processes. Finally, some new insights provided by the field of neuroscience with implications for conceptualizing mental disorders are presented.

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Introduction

We feel that ongoing discourse between mental health clinicians and neuroscientists is beneficial both for scientific progress in neuroscience and mental health treatments. Neuroscientists may benefit from being educated about clinical models of mental disorders and advances in the nosography of these disorders. The reductionist approach intrinsic to scientific activity forces neuroscientists to simplify their models in the pursuit of scientific questions considered to be of a fundamental nature. Unavoidably, at times, this approach may ignore some aspects of mental disorders. A discourse with clinicians allows neuroscientists to realign their models to ensure that they represent processes thought to cause or maintain these disorders.

Benefits to clinicians involve being informed of new research findings that have the potential to be applied in new pharmacological and nonpharmacological treatments. We provide two examples of how findings on memory, ie, reconsolidation and forgetting, may provide the impetus for new treatment interventions for several mental disorders. More generally, we believe that an elucidation of the memory processes not only provides clinicians with a list of potential clinical phenomena that could be the target of interventions, but it can also permit an understanding of why some kinds of treatments are more efficacious than others. In addition, our understanding of the memory processes can provide significant contribution to the refinement of extant psychotherapies, including cognitive behavioral therapy (CBT).

The aim of this review is to advocate how an understanding of the brain mechanisms involved in memory

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provides a basis for: (i) re-conceptualizing some of the mental disorders; (ii) refining existing therapeutic tools; and (iii) designing new ones for targeting processes that maintain these disorders. We start by defining some of the stages which a memory undergoes and discuss why an understanding of memory processing by the brain has clinical relevance. We then briefly review some of the clinical studies that have targeted memory processes. We end by discussing some new insights from the field of neuroscience that have implications for conceptualizing mental disorders.

Defining memory phases

Forgetting

As Ebbinghaus¹ demonstrated in his classic work, new memories can do one of two things; persist or be forgotten (*Figure 1*). It is generally assumed that forgetting is more a vice (ie, dysfunction) than a virtue (ie, constitu-

tive process). However, the idea that forgetting might be beneficial for memory has been frequently expressed.²⁻⁶ In the literary world, Jorge Luis Borges illustrated the essential role of forgetting for the human experience in his short story about Funes.⁷ As Funes could not forget anything, he could not live a normal life because a sea of unimportant details swamped every moment of awareness. We agree that, without constitutive forgetting, efficient memory would not be possible in the first place. Forgetting of established long-term memory (LTM) may indicate that memory is either physically unavailable (ie, lost), or that it is (temporarily) inaccessible. With some exceptions, theories proposed within the domains of experimental and cognitive psychology often emphasize one type of forgetting over the other.⁸ Two explanations for actual, nonpathological forgetting have been proposed; one involving decay of aspects of the memory trace, the other involving interference with it.^{9,10} Current consensus favors the latter of these two explanations for actual forgetting.

Notwithstanding the success of interference-based theories to describe the factors that promote forgetting, the truth is we do not know why or how the brain actually forgets.^{11,12} Recently, Hardt and colleagues have proposed a model of forgetting at both the cellular and systems level, and put forward a neurobiologically based framework for memory and forgetting.¹³ One inspiration for this framework is recent advances in the study of the cellular/molecular underpinnings of LTM persistence suggesting that memory decay is a major forgetting process.

One reason for this transition, in view of the nature of forgetting, is the finding that forgetting engages neurobiological mechanisms in the brain. In fact, the mechanisms implicated in forgetting overlap with the mechanisms implicated in learning and memory. For example, learning and memory have been suggested to be mediated by a nuanced neurobiological process that is initiated by calcium signaling from the N-methyl-D-aspartate (NMDA) receptor.¹⁴ At the cellular level, learning has been proposed to enhance the synaptic efficacy leading to long-term potentiation (LTP).¹⁵ The main hypothesis of the neurobiological instantiation of LTM is an increase in the number of: (i) presynaptic vesicles that are released¹⁶; (ii) post-synaptic receptors¹⁷; or (iii) synapse number.¹⁸ The post-synaptic receptors associated with LTM are thought to be actively maintained by a constitutive kinase called protein kinase zeta (PKM) as well as other putative memory maintenance molecules.¹⁹

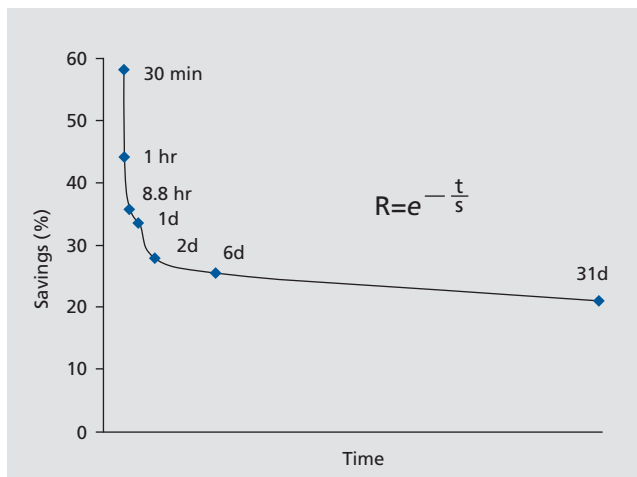


Figure 1. The forgetting curve. Herrmann Ebbinghaus famously conducted all experiments described in his seminal monograph "On Memory" with himself as the only subject. The data plotted in this curve are taken from the table on p 103.¹ It shows that the longer the time between learning and relearning a set of nonsense syllables, the more the original learning was forgotten. Importantly, most of the material was forgotten shortly after acquisition, followed by a reduction of curve acceleration. This type of relationship has been replicated in many species and for many different types of memories, and this research overall suggested that memory retention (R) over time can be described with an exponential function and negative acceleration (see inset). Despite significant research efforts, the neurobiological processes that underpin the forgetting function have not yet been described. R , memory retention; s , relative strength of memory; t , time

Forgetting can be prevented by NMDA receptor antagonists, which reverse the putative LTP induced by learning. These findings suggest that a core process involved in LTM maintenance prevents the internalization of receptors associated with forgetting. Since memory strength can increase with synaptic receptor expression,²⁰ forgetting may reflect the loss of the physical instantiation of the memory from relevant synapses. Thus, forgetting likely presents a biologically active process, rather than a shortcoming or failure of memory.¹³

Consolidation

There have been three lines of evidence to support the existence of a stabilization period of the order of hours after the acquisition of new memories. First, performance can be impaired if amnesic treatments such as electroconvulsive shock²¹ or protein synthesis inhibitors²² are administered after learning. Second, performance can be impaired if new competing learning occurs after the initial learning.²³ Third, retention can be enhanced by administration of various compounds, such as strychnine, after the initial learning.²⁴ Critically, all three manipulations are effective only when given shortly after new learning, not when given after a delay. These findings gave rise to theories of synaptic consolidation (*Figure 2A*).²⁵⁻²⁷ The initial unstable trace is called “short-term memory” (STM), with a duration of the order of hours. With time the trace enters LTM, at which point it is considered to be consolidated and can no longer be affected by treatments such as those listed above. Thus, if a memory is susceptible to enhancement or impairment, it is considered to be in a labile, nonconsolidated state, and if it is insensitive to administration of these amnesic treatments then the memory is, by definition, consolidated.^{26,28} Once a memory has become consolidated it remains in the fixed state and should be forever insensitive to future amnesic treatments.²⁶

Reconsolidation

Research on reconsolidation as another time-dependent restabilization processes was rediscovered with a paper by Nader and colleagues who demonstrated reconsolidation in a well-defined behavioral protocol (ie, auditory fear conditioning in the rat).²⁹ Targeting directly the brain circuitry that is critical in mediating behavior and its consolidation (ie, basolateral nucleus of the amy-

dala), and using a drug with well-documented amnesic effects on memory consolidation (ie, inhibition of protein synthesis with the antibiotic anisomycin), the authors showed that reminders could bring well-consolidated fear memories back to an unstable state; while in this state, these reactivated memories could be disrupted by inhibiting protein synthesis in the basolateral amygdala. Using the conceptual framework of the field of consolidation, the authors concluded that consolidated, but reactivated, memories return to an unstable state from which they must restabilize in order to persist (*Figure 2B*).³⁰

Since publication of this study, reconsolidation has been demonstrated with a range of species, tasks, and amnesic agents. The extant evidence for the existence of a reconsolidation process is once again based on the same three lines of evidence on which consolidation theory is rooted. First, performance can be impaired if amnesic treatments such as targeted infusions of protein synthesis inhibitors are given shortly after reactivation.^{29,31,32}

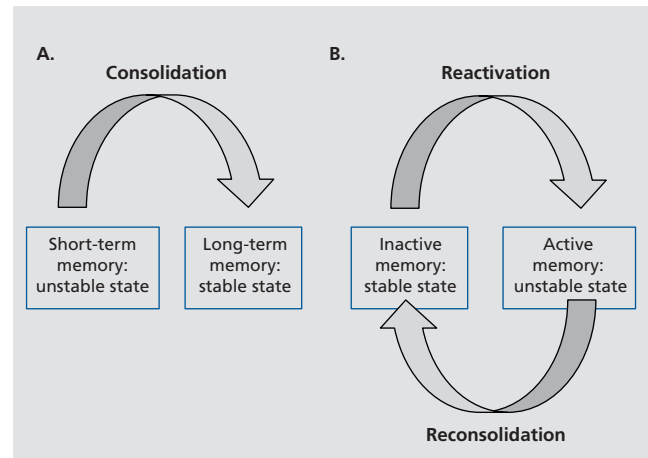


Figure 2. Principal properties of consolidation and reconsolidation. A) A textbook account of consolidation. New memories exist in an unstable state, during which their retention can be either enhanced or impaired. Over the next few hours memories are stabilized/consolidated over time into long-term memories, and once in that state, they remain fixed or permanent. B) A model of memory that incorporates the findings of consolidation and reconsolidation (proposed by Lewis, 1979). New and reactivated memories are in an active/unstable state and stabilize over time into an inactive memory state. Remembering may return inactive memories to an active state during which they can be enhanced or impaired again by similar pharmacological or behavioral intervention.

Adapted from ref 10: Lewis DJ. Psychobiology of active and inactive memory. *Psychol Bull.* 1979;86:1054-1083. Copyright © American Psychological Association 1979

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Second, performance can be impaired if new competing learning occurs in short temporal proximity to reactivation.³³ Third, retention can be enhanced by the administration of various compounds, such as activators of signaling pathways, important for consolidation after reactivation of the memory.³⁴ At the cellular and molecular level, a number of studies have demonstrated that blockade of reconsolidation of LTM leads to a reversal of molecular correlates of that LTM.³⁵⁻³⁷

A study by Lee demonstrated that neurons use consolidation mechanisms the first time a memory is acquired. For subsequent modification of the memory, including strengthening of the memory, neurons engage reconsolidation to stabilize the strengthening of the memory.^{38,39} One implication from this study is that memories rely on reconsolidation mechanisms throughout their lifetime. The brain engages consolidation mechanisms only during the initial memory storage.

Memory impairments induced by blocking reconsolidation can be relatively memory-specific. Indeed, only reactivated memories will be impaired.⁴⁰ From a therapeutic perspective, this means that when a patient is asked to recall, for example, a traumatic memory and then given an reconsolidation blockage agent, only that memory and not others will be blocked from being reconsolidated (ie, restabilized). While most of the therapeutic tools at the psychiatrist's disposal may have wide-ranging effects, the ability to target one memory at a time should be very good news for the field.

Clinical implications of reconsolidation

Why should clinicians care about the mechanisms mediating memory stabilization? As basic research scientists we need to explain how an understanding of the mechanisms of memory storage may shed light on the processes that maintain several mental disorders.

The fact is that memory phases and mechanisms are thought to be common for synapses representing a memory, the dysfunctional synapses that contribute to many disorders.¹⁴ The finding that consolidated memories return to a labile state and have to be restored has significant implications for a number of clinical conditions such as post-traumatic stress disorder (PTSD), addiction, obsessive-compulsive disorder (OCD), or delusions/hallucinations. An understanding of the mechanisms mediating reconsolidation could provide the basis for developing new or refining old therapeutic

tools to successfully manage, if not cure, some of these conditions. As an example of how this could be applied, imagine a patient with PTSD whose symptoms were resistant to both drugs and psychotherapy. A new way of treating this condition could be to reactivate the patient's traumatic memory and block its reconsolidation. Theoretically, this should lead to a "cure" within a single session. Although finding a cure in the removal of a memory in a single session may sound worthy of fiction, early studies on humans using electroconvulsive therapy (ECT) demonstrates that this possibility may not be incompatible with real life.

Franks and colleagues^{41,42} treated patients suffering from either hallucinations, delusions, major depression, or OCD. In contrast to other studies that administered ECT when the subjects were anesthetized, Rubin and colleagues kept the patients awake and directed them to focus on the objects of their compulsions or hallucinations. This experimental procedure reactivated the neural mechanisms mediating those memories when the ECT was delivered. All of the subjects were reportedly "cured" of their condition, even though some had had up to 30 previous ECT treatments while under anesthesia. The majority remained symptom-free for the 2-year period between the treatment and the publication of the manuscript. The fact that ECT was effective only when the memories were reactivated, but not when the memory reactivation was omitted (ie, when the patient was anesthetized), suggests in principle that reconsolidation occurs in humans. Furthermore, this study provides evidence that the possibility of curing someone by removing a memory in a single session may not be so remote.

Current treatments for PTSD and their possible limitations

Current psychological treatments of PTSD target mechanisms called extinction (*Figure 3*). After learning has occurred, the presentation of the conditioned stimulus (CS) elicits conditioned responses. Within the context of life-threatening situations, such as a car accident, the person learns to associate a certain stimulus with the possibility of death. Over time, any stimulus similar to the original stimulus (eg, a backfire of a car) can trigger the fear memory acquired during the exposure to the life-threatening situation. The person is again overcome with the traumatic experience of reliving the threatening sit-

uation, a process that is mediated by the amygdala.⁴³⁻⁴⁵ To learn that the new stimulus (ie, the backfire of a car) no longer announces death, the person should be exposed to the same stimulus in a safe environment over and over again. This procedure is referred to in the literature as “extinction learning.”⁴⁶ With time, the person will stop experiencing fear because the person has now learned that the stimulus no longer means threat or danger. However, since Pavlov, we have known that the expectation of threat is not lost, but that the fear upon being exposed to the stimulus is simply inhibited.^{46,47} We also now know that extinction learning is not nearly as robust as the initial learning to fear the stimulus. As such, the fear reaction can return any time, and often does within a few hours or days.^{46,47} In addition, if a similar stimulus is subsequently experienced in a new environment, the original fear can return.^{46,47} These properties of extinction learning may explain why treatments such as CBT for PTSD, which mostly rely on extinction learning as

therapeutic intervention, have only limited effectiveness. Extinction learning cannot inhibit the activation of these traumatic memories for long periods of time, and the benefits observed in the therapist’s office may not generalize to other contexts (Figure 4).

Given that extinction is not as strong a process as the traumatic memory, other neuroscientists proposed a modification that could make extinction learning more robust. The key to the method is the activation of the NMDA receptors with partial agonists such as d-cycloserine (DCS), which was found to enhance extinction learning.^{48,49} Davis and his colleagues suggested how DCS given prior to extinction of trauma should enhance the effect of CBT for PTSD.⁵⁰

Our concern with this revised extinction learning procedure is that a significant number of trials should be administered in order for DCS to enhance extinction of traumatic memory. If an insufficient number of extinction trials are administered, the memory will undergo reconsolidation. The effect of DCS on the fear memory when it undergoes reconsolidation is the enhancement of the fear memory (Figure 5).⁵¹ The only way to know

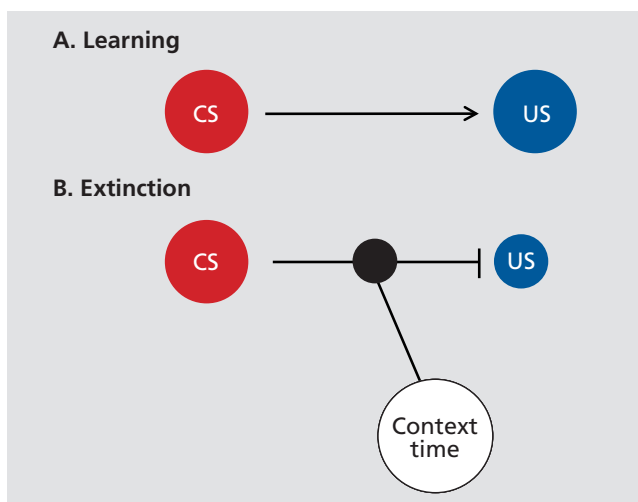


Figure 3. Schematic of learning and extinction processes. A) In conditioning, an association is learned between a conditioned stimulus (CS) and an unconditioned stimulus (US). CS and US can be of largely any modality; for example, a tone and a foot-shock. This learning will result in a conditioned fear response. B) Extinction was first reported by Pavlov. Extinction is considered new learning that inhibits the expression of the memory. It is much weaker than conditioning and results in a reduced conditioned response. For example, only one pairing of a tone and shock can lead to conditioned fear responses over the duration of an animal's life. Extinction takes many trials over time to reduce performance, and the reduction is rarely complete. Adapted from ref 108: Bouton ME, Nelson JB. Context-specificity of target versus feature inhibition in a feature-negative discrimination. *J Exp Psychol Anim Behav Process.* 1994;20:51-65. Copyright © American Psychological Association 1994

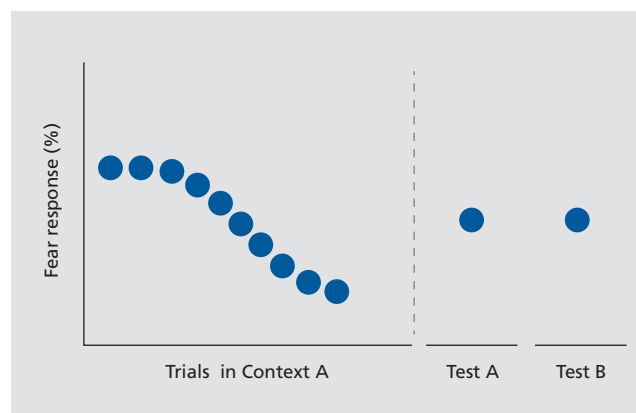


Figure 4. Schematic of extinction learning. Extinction trials entail presenting the conditioned stimulus (CS) in the absence of the unconditioned stimulus (US). With each CS presentation, the conditioned response is reduced as new learning occurs (CS no longer predicts the US). In animal studies, extinction always takes many more trials to inhibit performance than those required for its acquisition. The strength of extinction is typically reduced with time once an animal is removed from the extinction context. The amount of inhibition of the original memory decreases and the conditioned response is observed. This phenomenon is called spontaneous recovery (test A). Extinction learning is also reduced when animals are tested in a different context from the one in which they received extinction training (test B). This property is called renewal. There is no metric for how many extinction sessions are required for a certain percentage of responding.

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whether the memory has been extinguished is to administer real-time measures of fear levels during CBT. As most clinicians will not administer any measurement during treatments they may not know whether the memory has been extinguished enough to facilitate extinction. Based on the rodent studies, if not enough fear extinction learning has occurred DCS will make the traumatic memory stronger. Consistent with this hypothesis, a recent study in patients with generalized social anxiety reported that only those patients whose fear was low following the in-session exposure (significant fear extinction) benefited from DCS relative to those in the placebo condition (ie, no DCS but only exposure). In contrast, those patients in the DCS condition who reported high levels of fear (minimal fear extinction) following exposure were found to experience less clinical improvement than patients in the placebo condition.⁵² What may further complicate the treatment of PTSD patients (Figure 6) is that their neurobiology is in a state where the administration of the DCS plus CBT will lead

to the strengthening of their traumatic memory. Specifically, it has been known for some time that the brain areas associated with extinction are thought to be compromised in PTSD patients.⁵³ Indeed, a recent study by Milad and colleagues demonstrates that fear extinction learning was impaired in PTSD subjects.⁵⁴ The inability to extinguish fear memories is considered a core component of PTSD. Consequently, treatments that rely on the facilitation of extinction learning cannot easily take place because the brains of PTSD subjects do not acquire extinction. In the absence of extinction, CBT should induce reconsolidation, which in the presence of DCS should make the traumatic memory stronger. Two recent reports testing the effects of DCS on CBT found either no facilitation or reduction of the efficacy of CBT in PTSD consistent with our concerns outlined.^{55,56} Thus, for mental conditions that can undergo extinction learning, facilitated extinction may be a logical and exciting intervention tool. However, in the case of PTSD patients who do not show extinction, as there is nothing to facilitate, this tool may not be optimal.

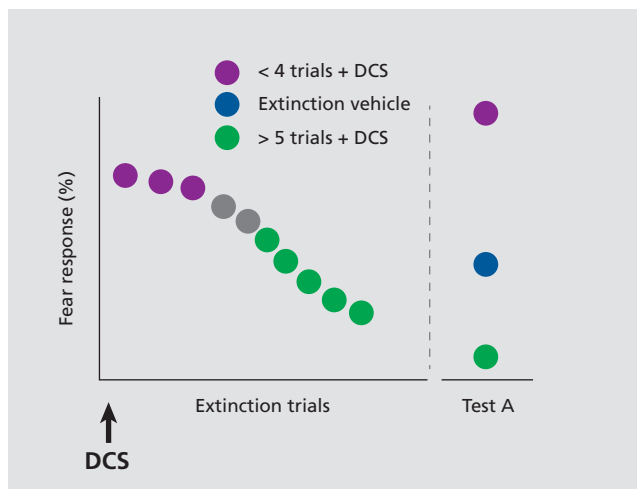


Figure 5. A schematic of the findings of Lee et al.⁵¹ If a fear memory is given enough extinction sessions to significantly reduce performance as shown in green, then D-cyclo-serine (DCS), a N-methyl-D-aspartate (NMDA) partial agonist can enhance extinction learning. In this case more than five extinction trials must be given to engage extinctions mechanisms before it can be enhanced. However, Lee also reported that DCS has the opposite effect if the number of trials does not induce significant extinction and the brain remains in a reconsolidation mode; the fear memory is enhanced. The number of trials required for the neurobiology to shift from reconsolidation to extinction mode is an empirical question for each memory and individual. Adapted from ref 51: Lee JL, Gardner RJ, Butler VJ, Everitt BJ. D-cycloserine potentiates the reconsolidation of cocaine-associated memories. *Learn Mem.* 2009;16:82-85.

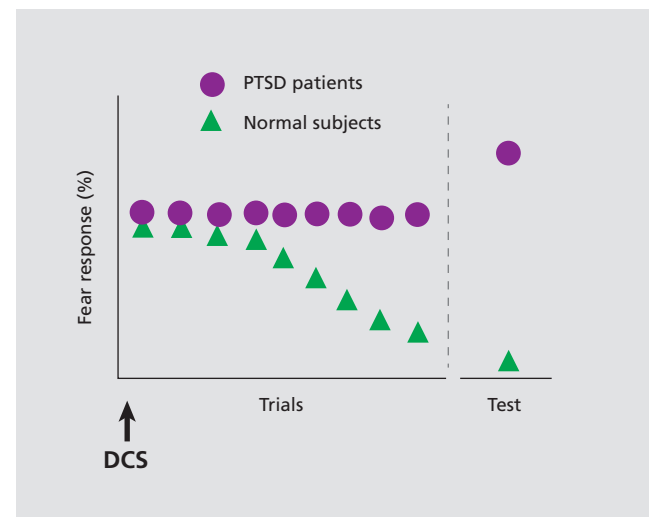


Figure 6. A schematic of why D-cyclo-serine (DCS) and cognitive behavioral therapy (CBT) should lead to stronger traumatic memories instead of facilitated extinction in PTSD patients. For common people with regular fears, CBT sessions will eventually shift the brain mechanisms from reconsolidation to extinction. If DCS is administered after extinction mechanisms are engaged, then the effectiveness of CBT should be enhanced. One of the defining features of PTSD is that patients are unable to extinguish fear memories. Thus, regardless of how many sessions of CBT are administered, the brain remains in reconsolidation mode, in which case DCS will not facilitate extinction, but rather enhance their traumatic memories.

Refining targets in the clinical population: the case of PTSD

PTSD is more than too much fear. Criteria for PTSD in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* acknowledge that fear is only one component of PTSD, and that its symptoms extend to a dysregulation of a variety of emotional states, including anger, guilt, and shame.⁵⁷⁻⁶⁰ Two pathways of emotion dysregulation, defined here as collectively referring to disturbances in a variety of emotional states, have been proposed in PTSD; one predominantly associated with adult-onset trauma, and the other related to repeated early life trauma.⁶¹ The first pathway suggests that mechanisms of fear conditioning and stress sensitization and kindling underlie emotion dysregulation experienced as a result of adult-onset trauma. Repeated sensitization to trauma-related stimuli may lead not only to a generalization of the fear response, but also to dysregulation of various emotional states through mechanisms comparable to kindling, which is a process that involves the development of generalized seizures following repeated, subthreshold electrophysiological stimulation. The intensification and broadening of emotional symptoms over time often observed in individuals with PTSD may be related to the original fear response becoming increasingly sensitized, thereby recruiting neighboring emotional circuits other than those involved in fear.⁶²⁻⁶⁴ In contrast, the second pathway focuses on the role of early developmental processes, including disruptions in the caregiver/infant attachment relationship, and early-life adversity in the development of emotion regulatory systems.⁶⁵ Such experiences may lead to an abnormal development of emotion regulatory capacities and thus reduce the effective regulation of fear arising from threatening or traumatic events. The latter can increase the risk of developing PTSD after trauma exposure later in life. These differential pathways to emotion regulation lead to the question of whether and how reconsolidation of traumatic memories may be affected by early-life experience. Future research examining the effects of early life adversity on processes of reconsolidation should therefore be carried out in both animal and human studies.

In the ideal case, altering the impact of the traumatic memory by reconsolidation blockade would result in restoring a patient's quality of life. However, other affective and social cognitive disturbances can remain, even

after successful treatment of core PTSD symptoms. A model proposing a social, cognitive, and affective neuroscience approach to PTSD which stresses the importance of assessing and treating not only PTSD symptoms, including traumatic memories per se, but also dysfunction in the domains of emotion regulation and interpersonal functioning, has been described.⁶⁶ In this regard, it is interesting to note that negative affect regulation and interpersonal problems accounted for a greater percentage of variance in functional outcomes than did PTSD symptoms in a sample of women with histories of childhood abuse.⁶⁷ In addition, cognitive deficits, including problems with executive functioning, and processing speed, as well as learning and memory, have been associated with PTSD.^{68,69} Future studies examining the effects of reconsolidation blockade in PTSD should therefore consider taking a broader assessment of outcome, including impairments in cognition, emotion regulation, and social cognition. The residual distance to normal reintroduction to society could be treated by CBT focusing on these additional domains.

Can propranolol change the course of PTSD when it targets consolidation of the traumatic experience?

The effects of propranolol have been examined in patients with a history of both acute traumatic experiences and chronic PTSD. With regard to acute traumatic experiences, in the first study examining the effects of propranolol following an acute traumatic event, Pitman and colleagues⁷⁰ recruited 41 patients who exhibited a pulse rate of ≥ 80 beats per minute from an emergency room (ER). Patients were randomized to receive either 40 mg of propranolol or placebo, first administered within 6 hours following the traumatic event during the putative time during which the memory is consolidated, and then for 10 days followed by tapering of the drug over 9 days. Results showed that 1 month following the traumatic event, individuals who had received propranolol exhibited a statistically nonsignificant trend towards lower Clinician Administered PTSD Scale (CAPS) scores and reduced physiologic responding as compared with the placebo group. A nonrandomized control study by Vaiva and colleagues⁷¹ examined 19 acute trauma patients with a pulse rate of ≥ 90 beats per minute recruited from an ER. Individuals were offered 40 mg of propranolol three times per day for 7 days, and

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PTSD symptomatology was compared in eight patients who agreed to take propranolol with 11 patients who declined the drug. Two months after the traumatic event, PTSD rates and symptoms were lower in the group who had received propranolol as compared with the group who had chosen not to take propranolol. Furthermore, a double-blind randomized controlled trial compared the effects of propranolol, gabapentin, or placebo in individuals admitted to a level 1 surgical trauma center. Propranolol was administered within 48 hours for a period of 14 days, including up-titration for 2 days at 60 mg daily, acute treatment 120 mg daily for 8 days, and tapering for 4 days.⁷² At 1- and 4-month follow-up, neither propranolol nor gabapentin led to superior outcomes in terms of PTSD and depressive symptoms. In the most recent randomized placebo-controlled study examining the effects of propranolol in 41 acutely traumatized individuals recruited from an ER, Hoge and colleagues⁷³ demonstrated no significant effect of up to 240 mg/day of propranolol administered for 19 days on PTSD symptoms assessed at 1 and 3 months post-trauma. However, in a subgroup of participants who exhibited high drug adherence, physiological reactivity during traumatic memory recall was significantly reduced 5 weeks post-trauma in individuals who had received propranolol as compared with placebo.

Can propranolol change the course of PTSD when it targets reconsolidation of the traumatic memory?

In patients with chronic PTSD, three open-label trials (n=28; n=7; n=32) have demonstrated that the administration of propranolol combined with reactivation of the traumatic memory led to a reduction in PTSD symptom severity by 50% to 56% and a decline in the rate of PTSD diagnosis of 71% to 86%.⁷⁴ Similar results were reported by Menzies in a study of 36 chronic PTSD cases⁷⁵ and an open-label trial by Poundja and colleagues.⁷⁶ However, placebo-controlled randomized control trials will need to confirm these results. Additionally, Brunet and colleagues⁷⁷ examined physiological responses in individuals with chronic PTSD in response to administration of propranolol or placebo subsequent to traumatic memory reactivation. Results demonstrated decreased physiological response to later traumatic memory recall with propranolol but not placebo. A striking finding in these studies is that a single reactivation

session was sufficient to induce reconsolidation in memories that were 30 years old.

In summary, even though data suggest that propranolol can reduce psychophysiological response associated with both recent and remote traumatic memories, its effect in PTSD symptoms per se, including reliving of the traumatic memory, avoidance symptoms, and emotional numbing, still requires further investigation. One of the core features of PTSD is that the traumatic memories are often reexperienced in the form of sensory flashbacks and are therefore not remembered but relived.^{78,79} To the best of our knowledge, no studies have investigated if the effects of propranolol extend beyond physiological effects, ie, altering the nature of how traumatic memories are recalled. Future studies examining the direct effect of propranolol on autobiographical memory recall are therefore warranted. Autobiographical memory recall has been suggested to play a key role in the experience of a continuous sense of self across time, and activation of the default mode network may be underlying this process since it has been shown to be active when individuals are engaged in internally focused or self-referential tasks, including autobiographical memory retrieval, envisioning the future, and theory of mind.⁸⁰ Patients with PTSD have been shown to have alterations in self-referential processing, including autobiographical memory recall,^{81,82} future-oriented thinking,⁸³ and theory of mind.^{84,85} Moreover, default mode network functioning which has been proposed to be the underlying mechanism of these interrelated processes has been shown to be altered in PTSD.⁸⁶⁻⁸⁸ The relationship between self-referential processing, in particular autobiographical memory recall, the default mode network, and brain networks involved in memory reconsolidation will therefore be an important avenue of future research.

Can reconsolidation blockade affect other mental disorders?

Substance addiction is a progressive psychopathology that leads to compulsive substance-taking behavior. Even after long periods of abstinence, relapse is quite common.⁸⁹ Cues in the environment that have acquired an associative relationship with substances are thought to contribute to substance taking and relapse.⁹⁰ There are at least two properties of cues associated with substances that could contribute to substance-taking behavior. First,

they can acquire rewarding and reinforcing properties unto themselves,⁹¹ Second, they can induce the resumption of substance-taking behavior (relapse).^{92,93} These cue-substance associations are very persistent and resistant to the extinction protocols used to decrease the strength of these conditioned responses in humans^{94,95} or animals.⁹⁶ Thus, in the clinic, extinction-based treatments have, to date, not been very effective.

Craving is also thought to be a process that mediates the effect of substance-related cues on relapse.^{97,98} Animal models of drug addiction have reported that the neurobiological mechanisms of craving undergo reconsolidation. When blocked, craving can reduce the ability of substance-related cues to induce relapse.⁹⁹ To date, targeting craving via reconsolidation blockage has shown to be the only short-term effective treatment (ie, one-time intervention) of relapse-prevention. Consequently, targeting reconsolidation of the mechanisms that mediate drug craving should increase the likelihood of long-term abstinence in humans.⁹⁰

Two elegant studies have reported the effects of targeting reconsolidation on craving mechanisms in opiate-¹⁰⁰ or cocaine-¹⁰¹ dependent drug users with amazing success. Using a behavioral procedure akin to interference, Xue¹⁰⁰ reported that craving in opiate addicts was reduced when reconsolidation was blocked. Similarly, propranolol decreased cocaine craving in addicts who had used cocaine for more than 20 years.¹⁰¹ However, the difference in craving was not long-lasting, as the experimental and placebo levels of craving were not statistically different 1 week after the intervention. One possibility for this absence of a difference is that propranolol impairment was transient. Another possibility, suggested by a visual inspection of the graphical presentation of the effect (*Figure 1*), is that the propranolol-induced impairment in craving is relatively constant. Future research should examine whether reduction in craving translates to a reduction in relapse rates and substance abuse.

Implications of forgetting for clinical practice: some speculative ideas

Constitutive forgetting may provide important functional contributions to the hippocampus. For example, the loss of hippocampus-dependent spatial and contextual memory may be instrumental for generalization effects and the development of schemas.¹⁰² On the other

hand, because systematic forgetting processes may control the life-time of memories, their deregulation could lead to accelerated and even pathological forms of memory loss, as seen in senescence and some dementias, such as Alzheimer's disease (AD). In the latter, β -amyloid causes increases in postsynaptic calcium, which promotes internalization and altered trafficking of synaptic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors, notably increased AMPA removal by engaging pathways involved in LTD.¹⁰³ This suggests that forgetting processes as described above may be involved in the pathology of AD, and the accelerated forgetting of episodic content typical for the disease might drive the autobiographical impairment and eventual loss of a self-narrative.

It is thus possible that the eventual synapse loss and cell death, which characterize the final stages of AD, are driven in part by forgetting processes that spiral out of control. Traditional views of AD assume that dementia is the result of neuron death or dysfunction in the affected areas. While provocative but possible, one explanation for this condition is that uncontrolled forgetting maybe be one of the mechanisms leading to cell dysfunction and death.

Therapeutic approaches could therefore target certain steps in molecular pathways associated with forgetting, and possibly at time points well before the devastating stages of the disease manifest. Drugs that affect the synaptic removal of AMPA receptors might prove effective in preventing steps that eventually lead to synapse deterioration, as synapse stability critically depends on the glutamate (GluA2) and AMPA receptors.¹⁰⁴ In animal models, it has been shown that the peptide GluA23Y, which competitively prevents internalization of GluA2-dependent AMPA receptors, can prevent long-term depression, a possible physiological model of plasticity mechanisms involved in forgetting.³⁷ Thus, developing methods to delivering GluA23Y either targeted to specific brain areas or systemically might slow down the progression of synaptic loss and memory deterioration.

Forgetting and psychotic dissociations

In light of the likely involvement of NMDARs in constitutive forgetting processes, we speculate that inhibited forgetting might contribute to the development of psychotic symptoms. For example, ketamine, an NMDA

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antagonist, can induce psychotomimetic states in humans and can worsen symptoms in patients with schizophrenia.¹⁰⁵ Additionally, animal models of psychosis are based on NMDAR antagonism in the hippocampus.¹⁰⁶ It may be possible that with significantly reduced constitutive forgetting that removes the vast majority of random memories encoded during wake states,¹³ the system approaches states resembling intensified interference, in which memory formation is greatly impaired, and which can lead to the loss of previously established memory patterns. This could lead to dissociative states as a consequence simply of the inability to encode new experiences.

Conclusion

Memory is a dynamic process. In so being, it provides clinical targets for the treatment of mental disorders, such as forgetting and reconsolidation. As our understanding of forgetting grows, there may be better tools

to target and to slow down forgetting in certain dementias, such as Alzheimer's disease. Reconsolidation has basic implications for a wide variety of mental disorders, not just PTSD. The fact that reconsolidation can operate on extremely strong and old memories¹⁰⁷ presents extremely exciting therapeutic prospects. Thus, reconsolidation can provide clinicians with a time window of instability to modify the neural circuits mediating mental illness. The advantage of this approach is that one does not need to first identify the specific neuroscientific bases for each mental disorder before designing a treatment for it. As Rubin's studies demonstrate, allowing memory states to be expressed was sufficient to return circuits mediating mental disorders to become "unstored." There are many such tools available for blocking the restorage of reactivated memories, ranging from behavioral to pharmacological methods. □

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La memoria como un nuevo blanco terapéutico

Esta revisión busca demostrar cómo una comprensión de los mecanismos cerebrales involucrados en la memoria aportan las bases para: 1) reconceptualizar algunos trastornos mentales, 2) perfeccionar las herramientas terapéuticas existentes y 3) diseñar nuevas terapias para los procesos clave que sustentan estos trastornos. Primero se definen algunas de las fases que están a la base de la memoria y se discute la relevancia clínica de la comprensión de los procesos de memoria por el cerebro. Luego se revisan brevemente algunos estudios clínicos que se han enfocado en procesos de memoria y finalmente se presentan algunas nuevas perspectivas provenientes de las neurociencias que tienen repercusiones para la conceptualización de los trastornos mentales.

La mémoire comme nouvelle cible thérapeutique

Cet article démontre comment la compréhension des mécanismes cérébraux impliqués dans la mémoire sert de base à : a) reconceptualiser certains troubles mentaux; b) améliorer les outils thérapeutiques existants ; et c) élaborer de nouveaux outils pour cibler les processus qui entretiennent ces troubles. Nous définissons tout d'abord certains des stades par lesquels passe la mémoire, et nous analysons la pertinence clinique du traitement de la mémoire par le cerveau. Nous poursuivons par une brève mise au point de quelques études cliniques sur les processus mnésiques. Nous présentons enfin les nouveautés dans le domaine des neurosciences et leurs conséquences dans la conceptualisation des troubles mentaux.

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